Original claims 1-3 and 7-20, are pending in the application, claims 4-6 having been cancelled previously. Applicants are pleased to acknowledge that claims 19 and 20 have been deemed to recite allowable subject matter such that only a single rejection remains regarding claims 1-3 and 7-18, under 35 U.S.C. §112, first paragraph, for lack of enablement.

During the interview of April 29, 2002, at which the Examiner, Dr. Prockop, and the undersigned were in attendance, it was agreed that, with regard to the enablement rejection, evidence regarding the usefulness of specific animal models for Parkinson's disease (PD), stroke, ischemia and spinal cord injury (SCI) in predicting effective treatment in humans would strengthen Applicants' arguments that claims 1-3 and 7-18 are enabled with regard to these CNS diseases. Further, during the interview, Applicants averred that post-filing reduction to practice demonstrates enablement relating to treatment using differentiated cells thereby supporting claims 16 and 17.

Applicants respectfully submit, as more fully set forth below, that the enablement rejection has been overcome and that evidence demonstrating treatments effective in animal models, which were also effective in humans, as well as evidence that differentiated cells can be used in the methods of the invention, has been provided herein. In accordance with the agreement memorialized in the Interview Summary of April 29, 2002, Applicants aver as follows.

Rejection of Claims 13 and 7-18, Under 35 U.S.C. § 112, first paragraph

Claims 1-3 and 7-18 stand rejected under 35 U.S.C. § 112, first paragraph, because in the Examiner's opinion, cell and gene therapy using marrow stromal cells are not enabled by the disclosure in the specification given the unpredictability of the art at the time of filing. Applicants have previously addressed this rejection in Responses to previous Office Actions, which Responses were filed on February 10, 2000 (responding to Office Action mailed October 4, 1999; Paper No. 6), November 20, 2000 (responding to Office Action mailed May 24, 2000; Paper No. 12), and by arguments presented by way of Preliminary Amendment and accompanying Declaration of co-inventor, Darwin J. Prockop, pursuant to 37 C.F.R. 1.132 ("the Declaration"), filed on August 31, 2001. Applicants hereby incorporate by reference the arguments set forth in those Responses as if set forth in their entirety herein.

Applicants had previously presented data and arguments supporting that post-filing reduction to practice demonstrates that MSCs have been used in gene therapy to successfully treat Parkinson's disease in an art-recognized animal model (*e.g.*, unpublished thesis of Emily J. Schwarz, Exhibit "B" of the Declaration), and in cell therapy to treat SCI, stroke and ischemia also in art-recognized animal models of these diseases (*see, e.g.*, Chen 2001; Li 2001; Olson, 2001; and Chopp 2001, all cited in the Declaration). Nonetheless, the Examiner argues that the references do not demonstrate sufficient enablement and/or that these references do not demonstrate that success in animal models is sufficiently correlated with success in human disease. Applicants respectfully submit that these and other post-filing reduction to practice demonstrates that MSC treatment of CNS disease is enabled in art-recognized animal models of PD, stroke, ischemia and SCI. Applicants further submit that previous treatments identified and/or developed in such art-recognized animal models correlated with successful treatment of human disease.

It is well-settled that an Applicant need not have actually reduced the invention to practice prior to filing. MPEP §2164.02 (citing *Gould v. Quigg*, 822 F.2d 1074 (Fed. Cir. 1987)). Indeed, the invention need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908 (C.C.P.A. 1970). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)). Therefore, under current law, enablement does not require a working example and experimentation is allowed so long as it is not undue.

At page 4 of the Office Action, the Examiner argues that the specification does not provide sufficient guidance as to how to treat a human patient in that, *inter alia*, the specification does not disclose any disorder which has been subjected to the claimed regimen. Preliminarily, one embodiment of the invention is to use cells derived from a patient's own bone marrow to treat the patient, which is analogous to bone marrow transplantation, a therapy that

has saved hundreds of thousands of lives over the last 20 years (*see*, Craddock, 2000, Lancet Oncol. 1:227-234; Saba and Flaig, 2002, J. Hematother. Stem Cell Res. 11:377-387). Secondly, the strategy of the invention is also analogous to a therapy used for over 10 years for the therapy of parkinsonism, *i.e.*, implantation of neural tissue from the brains of human fetuses into the striatum of human patients. The neural tissue therapy has produced good results in some patients (*see, e.g.*, Bjorklund et al., 1980, Brain Res. 199:307-333; Bjorklund et al., 1992, Curr. Opin. Neurobiol. 2:683-689; Widner et al., 1992, New Eng. J. Med. 327:1589-1590; Dunnett et al., 1981, Brain Res. 229:209-217; Wictorin et al., 1992, J. Comp. Neurol. 323:475-494; Piccini et al., 1999, Nature Neurosci. 2:1047-1048; Piccini et al., 2000, Ann. Neurol. 48:689-695). The present invention, while similar to these prior art treatments, provides a significant improvement in that MSCs were not used for those treatments. Thus, the present invention overcomes prior art limitations in that, among other things, some patients did not respond to prior art therapies, in part because fetal neural tissues are not as available as MSCs and therefore less tissue can be implanted. Also, the present invention overcomes prior art limitations of bone marrow transplantation and fetal neural tissue implantation because in the prior art therapies the MSCs are not removed by immune responses (*compare* Lopez-Lozano et al., 1997, Transplant Proc. 29:977-980 *with* Schwarz et al., ISHAGE 2001, Abstract). The present invention teaches use of MSCs which overcomes these prior art limitations since MSCs are derived from the patient being treated and can be readily grown to produce sufficient quantities of cells. Nonetheless, while the present invention overcomes prior art hurdles, the methods of the present invention are sufficiently analogous to the cell therapies of bone marrow transplantation and fetal neural tissue implantation to support that the methods of the present invention are enabled for purposes of Section 112, first paragraph.

Therefore, even assuming, *arguendo*, that as the Examiner argues, the specification does not provide any specific disorder which has been subjected to the claimed treatment or any specific methodology associated with the treatment, the treatment is sufficiently analogous to prior art methods that the skilled artisan would have understood, based upon the teachings of the invention, including, but not limited to, the use of MSCs, how to practice the invention commensurate with the scope of the claims without undue experimentation. This is because, as pointed out in previous responses filed in this application, the level of skill in the art was high and the art routinely engaged in such experimentation, which was thus not undue under

the present law of enablement.

In any event, the specification does provide specific methodology, in that, for instance, it teaches that the MSCs are administered so that they reach the site of damage to nervous tissue (specification at page 15, lines 4-13). Indeed, the specification demonstrates the successful reduction to practice in that Example 7 discloses the implantation of MSCs in the brain (specification at page 47, line 8, to page 53, line 12). Thus, the skilled artisan, based upon the teachings of the invention, would have been able to implant the cells and practice the methods of in the invention without undue experimentation since the one of ordinary skill would have known, at the time the specification was filed, to practice the methods using only the experimentation regularly exercised in the art to do so.

The Examiner further contends that the specification does not disclose the specific number of cells to be administered for each disease. However, this is not relevant where one skilled in the art would have appreciated, based upon the teachings of the specification as filed, that initial clinical trials could be performed by simply adjusting cell numbers used in the animal model disclosed in the invention by factoring in, among other things, the weight and age of the patient, as routinely performed in the art. Also, standard formulas for testing increasing dose levels are used in FDA prescribed Phase I of clinical trials and the skilled artisan routinely determined such dosages such that doing so would not be undue experimentation. Thus, it would not have been undue experimentation for the skilled artisan, armed with the teachings of the invention, to determine, by experimentation typically carried out in the art, the number of cells to be used for a particular treatment. Such experimentation, even if complex, was not undue since the skilled artisan typically engaged in it.

The Examiner also argues that the specification does not disclose the route of administration for each disease (Office Action at page 4). Even assuming, for argument's sake, that the specific route of administration was not disclosed in the specification as filed and that somehow this was required for enablement under Section 112, one of skill in the art would have understood that various methods could be used to practice the invention. These administration routes include, but are not limited to, infusion directly into the site of tissue damage or into the cerebral spinal fluid as was disclosed in several reports on models of spinal cord injury (Honmou et al., 2001, Annual Meeting of the Society of Neuroscience, San Diego, CA, November 10-15, 2001, Abstract; Ankeny et al., Annual Meeting of the Society of Neuroscience, San Diego, CA,

November 10-15, 2001, Abstract; Hofstetter et al., 2002, Proc. Natl. Acad. Sci. USA 99:2199-2204; Wu et al., 2002, Neuroscience Letters 318:81-84; Chopp et al., 2000, Neuroreport 11:3001-3005), administration to the striatum, which is the major site of depletion of the neurotransmitter dopamine in parkinsonism and therefore as was done in the models for parkinsonism using either viral vectors (During et al., 1994, Science 266:1399-403; Mandel et al., 1998, J. Neurosci 18:4271-4284) or MSCs (Schwarz et al., 1999, Human Gene Therapy 10:2539-2549).

Additionally, the skilled artisan would have appreciated, based upon the disclosure provided in the specification as filed, that the cells can be administered intravenously or intra-arterially, routes that might be most useful for some patients, particularly those in which a disease process has partially broken down the blood-brain barrier (Lu et al., 2001, J. Neurotrauma 18:813-819). Accordingly, the skilled artisan, armed with the teachings of the invention, would have understood that the route of administration depended on the site of injury, the disease being treated, and the like, and would have determined the route of administration without such experimentation being undue because the art typically engaged in it.

The Examiner further contends that the specification as filed does not teach the relevant cell therapy target site for the specific disease. Applicants respectfully submit that the specific target site is disclosed and is the site of tissue injury and the MSCs can be administered by several different routes to reach it as more fully set forth previously elsewhere herein. Therefore, no undue experimentation would be required where the site of injury is the target site for the disease and the routineer would not require any experimentation not routinely practiced in the relevant art to determine that target site.

Further, the Examiner argues that the specification does not disclose any specific therapeutic gene to be used in practicing the invention (Office Action at page 4). As stated previously elsewhere herein, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. Applicants respectfully submit that for each disease, genes for proteins or metabolites that are known to be deficient, or genes for products known to stimulate repair of nervous tissue, are known and the subsequent post-filing reduction to practice has demonstrated their use. For instance, in the case of parkinsonism, genes for tyrosine hydroxylase and GTP cyclohydrase have been used in viral vectors (During et al., 1994, Science 266:1399-403;

Mandel et al., 1998, J. Neurosci 18:4271-4284) and in MSCs (Schwarz et al., 1999, Human Gene Therapy 10:2539-2549). In another example, in the case of spinal cord injury (Himes et al., 2001, J. Neurosci. Res. 65:549-564) and stroke (Andsberg et al., 2002, Neurobiol. Dis. 9:187-204), genes for cytokines and neurotrophins have been used in fibroblasts (Himes 2001) or viral vectors (Andsberg 2002). Therefore, where the gene(s) associated with the disease are known, the specific therapeutic gene to be used to practice the invention is known to the skilled artisan and no undue experimentation is required.

The Examiner then argues that at the time of filing, the state of the art taught that the therapeutic effectiveness were neither routine nor predictable, citing Prockop (1994, Science 276:71-74), Gerson (1999, Nature Med. 5:262-264), and Sanberg et al. (1998, Nucl. Acids Symp. Res. 38:139-142). Applicants respectfully submit that as more fully set forth elsewhere herein, many of the issues discussed by Prockop, and Gerson have been resolved by subsequent post-filing reduction to practice following the teachings disclosed in the specification as filed, as demonstrated by the references provided herewith.

Additionally, the Examiner, at page 5 of the Office Action, cites Sanberg et al. (1998, Nucl. Acids Symp. Ser. 38:139-142) to support that "perhaps the most serious problem faced in the field of cell transplantation is that of host generated immune response to the graft tissue." While this may be an important objection to direct administration of viral vectors to patients, these concerns are not particularly pertinent to the present invention. This is because the data disclosed in the specification as filed demonstrate that the cells of the invention are not rejected by the immune system even where the donor cells were from a different species than the recipient. More specifically, the data disclosed in the specification as filed demonstrate that human MSCs transplanted into rat brains engraft and are not rejected. Thus, where the cells of the invention are not immunogenic when transplanted into the CNS, the concerns of Sanberg et al. are particularly irrelevant. Also, any therapeutic genes will produce proteins or metabolites that are native to the patient such that no immune response is generated to the therapeutic protein produced. Therefore, there is no basis for suggesting that any immune responses will be encountered using the methods of the invention, and Sanberg et al., is not applicable to the present invention.

The Examiner also contends that it is more difficult to use cell transplantation to treat diseases where neurons die, such as stroke, using cell transplantation. Even assuming,

arguendo, that it is more difficult to treat diseases where extensive cell death has occurred throughout the brain, Applicants submit that post-filing reduction to practice demonstrates that MSCs can repair tissues in which neuronal cells are dead or dying. Without wishing to be bound by any particular theory, it may be that two mechanisms play a role in treatment where cell death has occurred: either the MSCs can become new astrocytes and probably oligodendrocytes and neurons (Kopen et al., 1999, Proc. Natl. Acad. Sci, USA 96:10711-10716; Woodbury et al., 2000, J. Neurosci. Res. 61:364-370) and/or the MSCs can provide a microenvironment that rejuvenates damaged and dying neuronal cells (Ankeny et al., Annual Meeting of the Society of Neuroscience, San Diego, CA, November 10-15, 2001, Abstract; Hofstetter et al., 2002, Proc. Natl. Acad. Sci. USA 99:2199-2204). Therefore, based on post-filing reduction to practice and the disclosure provided in the specification as filed, there is ample support to enable that MSCs can have beneficial effects even in conditions in which neuronal cells are dying.

Further, the Examiner contends that Sabate et al. (1996) caution that there are several important issues to be resolved before gene therapy for neurological diseases is to become a reality" thus indicating the unpredictability of the art at the time of filing. While the issues discussed by Sabate et al., have been recognized as important considerations for methods relating to gene therapy using viral vectors in patients (*in vivo* gene therapy), these issues are largely obviated by using either unmodified MSCs or MSCs genetically modified or differentiated before administration to the patient, as proposed in the present invention. More particularly, three of the five issues enumerated by Sabate et al. only apply to the special case in which the MSCs are modified to express a transgene (*in vitro* therapy), while in the present invention these are far less serious concerns than in therapies in which viruses are directly administered to patients.

Specifically, "the extent of transgene expression" is not a major concern in the present invention because the expression can be accurately assayed by anyone skilled in the art before administration of the cells to the patient (*ex vivo* therapy). Further, the "stability of transgene expression" is much less of a concern with MSCs than with viral *in vivo* therapy, because the transgene can be introduced into the MSCs using a variety of techniques that include viruses (self-inactivating) that delete their own viral sequences as they are incorporated into the cells so that the MSCs will not contain the viral sequences that target transgenes for inactivation

(Schwarz et al., 2001, Gene Therapy 8:1214-1223), and/or using physical techniques such as electroporation in which naked genes without any viral sequences are used and using large gene constructs that include large promoter regions of the native gene can be used (Keating et al., 1990, Exp. Hematol. 18:99-102).

Another concern discussed in Sabate et al. raised by the Examiner, *i.e.*, "targeting of cells," is not a significant problem in practicing the methods of the present invention because in gene modified MSCs, the gene will be targeted and the extent of targeting can be accurately assayed by anyone skilled in the art before the cells are administered to a patient. Also, the targeting of MSCs in patients is greatly simplified by the fact that the cells have an innate ability to target themselves to sites of tissue injury and repair the injury (Pereira et al., 1998, Proc. Natl. Acad. Sci. USA 95:1142-147; Kotton et al., 2001, Development 128:5181-5188). The issue of "safety of the procedure" raised by Sabate et al., is a minor concern in the present invention because, as more fully set forth elsewhere herein with regard to Sanberg et al., the present invention does not require the use of virus vectors, and the cells were not immunogenic even where the donor/recipient crossed species barriers much less when the cells administered are obtained from the patient being treated and are the patient's own MSCs that are part of his/her own natural repair system. Indeed, more recently, Dr. Prockop and colleagues have demonstrated successful transplantation of allogeneic MSCs in adult rat brains (Schwarz et al., 2001, Abstract presented at ISHAGE 2001, June 14-17, 2001). Additionally, clinical trials have already demonstrated that MSCs produce no adverse reactions when infused in large numbers intravenously in patients. "Vector large-scale production capacity" is not a consideration with genetic modification of MSCs because even when virus vectors are used for *in vitro* therapy, anyone skilled in the art will need only a small amount of vector to transduce a small number of MSCs. The transduced MSCs then can be expanded extensively in culture before administration to a patient. Finally, "inflammatory responses" are not a concern in the present invention since adenoviruses and other viral vectors need not be used. Also, no immune or inflammatory responses were detected even when human MSCs were infused into mouse brains (Azizi et al., 1998, Proc. Natl. Acad. Sci. USA 95:3908-3913), demonstrating that the cells are not antigenic even where the transplantation crosses species boundaries. Moreover, allogeneic transplantation in rat brains also demonstrated successful engraftment of MSCs (Schwarz et al., ISHAGE 2001 Abstract). Therefore, where immunogenic virus vectors need not be used, where the patient's

own cells can be transplanted, and where the cells are not immunogenic even where species boundaries are crossed, the concerns of Sabate et al., are not relevant to the present invention.

On page 6, citing Sabate et al., the Examiner notes that recombinant adenoviruses can lead to severe inflammatory responses." Again, as indicated previously elsewhere herein, immune and/or inflammatory responses are not relevant objection to the use of MSCs which are taken from the patient and then reintroduced into them thus obviating any immune response, nor are they a concern where recombinant adenoviruses are not used. Further, inflammatory responses are not even a concern where the cells are derived from a different species, much less when the donor is a human and the cells are transplanted into a human recipient.

The Examiner argues at page 7 of the Office Action, that the specification does not cite tyrosine hydroxylase and GTP cyclohydrases for parkinsonism. As stated previously elsewhere herein, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. The involvement of L-DOPA in parkinsonism, as well as the metabolic pathway for the biosynthesis of L-DOPA, were well known to one skilled in the relevant art at the time the specification was filed. Thus, use of these two genes to treat Parkinson's would have been apparent to anyone skilled in the art; indeed, these two genes were used by others with viral vectors in animal models for parkinsonism (Mandel et al., 1998, J. Neurosci 18:4271-4284). Therefore, Applicants were not required, for purposes of enablement, to specifically include the genes for L-DOPA synthesis, or for the expression of any other known therapeutic protein, where the genes were known at the time of filing and where the importance of the genes in treating the disease, *e.g.*, parkinsonism was appreciated at the time of filing.

The Examiner further argues that the invention is not enabled because the unmodified MSCs did not work in publication by Schwarz et al. However, the reported experiments were a single trial with a single dose and a single time point for infusion of MSCs. Therefore, the results do not rule out the possibility that unmodified MSCs will be effective under slightly different conditions such as repeated administration of the cells. Indeed, unmodified MSCs were successfully used to treat osteogenesis imperfecta (OI) in both an art-recognized animal model (Pereira, 1998) and in humans (Horwitz, 1999). Thus, there is evidence that cell therapy using unmodified MSCs can be used to effectively treat disease in humans.

The Examiner dismisses the success demonstrated for treatment of OI using MSCs at page 8 of the Office Action stating, in part, that, "connective tissue cells are not required to form synapses." Applicants respectfully point out that MSCs are not connective tissue cells. However, MSCs can differentiate into other cells lineages that include cardiomyocytes, lung pneumocytes, astrocytes, and neurons. Thus, the example that MSCs can be used to treat OI is not limited solely to connective tissue diseases; rather, the stem cell qualities of these cells make them useful for treatment of CNS diseases as well.

The Examiner then contends essentially that results obtained using such animal models are unlikely to be applicable to human subjects. That is, despite the working example demonstrating that results obtained in a non-human animal model of OI correlated to results obtained in humans, the Examiner argues that art-recognized animal models of disease are not predictive of human diseases.

Applicants respectfully submit that art-recognized animal models of CNS disease have been used to develop effective therapies for human patients. More specifically, the same rat model for parkinsonism employed by Schwarz et al. (1999) was used to develop the use of L-DOPA for the treatment of this disease (Ungerstedt et al., 1974, Advances in Neurobiol. 5:421-426), and is still the most effective therapy for it (Danisi, 2002, Geriatrics 57:46-50). The same rat model for parkinsonism was also used to develop the therapy for the disease based on the infusion of fetal brain tissue (Bjorklund et al., 1980, Brain Res. 199:307-333; Bjorklund et al., 1992, Curr. Opin. Neurobiol. 2:683-689; Dunnett et al., 1981, Brain Res. 229:209-217; Wictorin et al., 1992, J. Comp. Neurol. 323:475-494), a second therapy that is effective in some but not all patients (Widner et al., 1992, New Eng. J. Med. 327:1589-1590; Piccini et al., 1999, Nature Neurosci. 2:1047-1048; Piccini et al., 2000, Ann. Neurol. 48:689-695).

Furthermore, the art-recognized animal models of spinal cord injury used to test MSCs in the present invention are the same models that were used to develop progesterone therapy for spinal cord injury (Labombarda et al., 2002, J. Neurotrauma 19:343-355), which therapy is the only current successful therapy for treating SCI in humans (Dumont et al., 2001, Clin. Neuropharmacol. 24:265-279).

Additionally, the same art-recognized animal models for stroke used to test MSCs and to demonstrate the reduction to practice of the invention are the very same models that were used, and which are still being used (De Cristobal et al., 2001, J. Neurochem. 79:456-459), to

develop drugs that prevent platelet aggregation, currently the most effective therapeutic agents for treatment of strokes in humans (Dogne et al., 2002, Curr. Med. Chem. 9:577-589).

These data demonstrate that despite the Examiner's assertions to the contrary, these art-recognized animal models for Parkinson's disease, SCI and stroke have withstood the test of time as being extremely useful in developing new therapies for these diseases and for predicting the usefulness of therapies in human patients. Thus, the data demonstrate that these art-recognized animal models of CNS disease are highly predictive of useful treatments for use in humans. For these reasons, the positive results obtained to treat Parkinson's disease, stroke and SCI using MSCs in such animal models are highly likely to be applicable to human subjects.

The Examiner, at page 9 of the Office Action, disputes the findings disclosed in several references cited by Applicants in a previous response to demonstrate that MSCs have been used successfully in art-recognized animal models of CNS disease. More particularly, the Examiner contends that Li teaches treatment of stroke by intracarotid administration of MSCs whereas the present invention does not contemplate such route of administration such that Li does not support enablement of the present invention. Applicants respectfully point out that one skilled in the art would have tried this route of administration in addition to others. Thus, it would not have been undue experimentation for one skilled in the art to attempt various routes of administration, including, but not limited to, intracarotid administration of MSCs.

Additionally, the Examiner contends that "Olson fails to teach any type of therapeutic effect." Applicants respectfully submit that a more recent publication describing the Olson et al. experiments in detail, demonstrates a therapeutic effect (Hofstetter et al., 2002, Proc. Natl. Acad. Sci. USA 99:2199-2204). In brief, rats were injured with an impact injury of the spine. Of 10 control rats, none could lift their trunks from a flat surface because of paralysis of the hindlimbs. Of 12 rats treated with MSCs infused into the spinal cord, 7 could lift their trunks. Also, the treated rats performed at a statistically better level in the BBB behavioral test that is a standard measure of motor performance in rat models for spinal cord injury. Thus, post-filing reduction to practice demonstrates that MSCs can be used to treat SCI as demonstrated in an art-recognized animal model and where the model has been demonstrated to be predictive of treatments for humans.

The Examiner also contends that in several figures from papers cited publications by Chen (2001), Li (2001), and Chopp (2000), "the standard deviation of the results in the

transplanted animals overlaps the standard deviation of results from control animals." Applicants respectfully point out that these authors state that their results are statistically significant and that the data were published in peer reviewed journals. Without access to the original data there can be no basis for challenging their published results. While some tests for functional improvements in models for central nervous system diseases show large variances, the tests have been effectively employed by many investigators for many years and they have been shown to be good predictors of favorable therapeutic benefits in patients. It is well recognized in the field that the behavioral tests have proven to be particularly predictive of effects in patients if similar results are obtained by more than one laboratory. Therefore, it is important to note that Hofstetter et al. did obtain statistically highly significant results in the rat model for spinal cord injury. These results as well as those of Honmou et al. on improved myelination of the spinal cord, and Ankeny et al. on behavioral improvement in rat models for spinal cord injury, provide independent support for the conclusion that MSCs are effective in repairing damaged tissues of the central nervous system.

The Examiner then argues that Chen et al. teach intravenous delivery of MSCs and Li et al. teaches intraarterial delivery and that intraarterial delivery of MSC is superior. Applicants respectfully submit that as discussed previously elsewhere herein, one skilled in art typically attempted various routes of administration and such experimentation was not undue in the relevant art. Thus, those skilled in the art would have tested several routes for delivery of MSCs to the site of injury of the central nervous system, and the teachings of Chen and Li demonstrate the high level of skill in the art, the complexity of experimentation routinely engaged in by the skilled artisan, and that MSCs can be delivered using various routes to the site of injury where they provide treatment for various CNS diseases in art-recognized animal models that are highly predictive for effective treatments for humans. Nothing in Chen or Li suggest that the methods of the invention are not enabled, on the contrary, Li and Chen support that the present invention is amply supported.

The Examiner, at page 10 of the Office Action, contends that the teachings of Li, Chopp and Chen cast further doubt on the enablement of claims 16 and 17. That is, in the Examiner's view, Chen, Li, and Chopp do not teach the delivery of differentiated cells. Instead, the Examiner reasons that each of these publications indicates that the likely mechanism is secretion by MSCs of cytokines and growth factors, and that there is no evidence of record that

MSCs differentiated would secrete factors. Applicants respectfully submit that even assuming, *arguendo*, that Li, Chen and Chopp do not support that differentiated MSCs can provide therapeutic benefit in CNS disease, several other references demonstrate the usefulness of differentiated MSCs for treatment of CNS diseases. Specifically, Schwarz et al. (1999) and Schwarz et al. (2001) demonstrated that MSCs are differentiated by transfection with two genes to secrete L-DOPA. Therefore, these cells can be regarded as partially differentiated to dopaminergic neurons and they still secrete a neurotransmitter. Thus, the differentiated MSCs of Schwarz et al., demonstrate that these cells can be used to treat parkinsonism.

Further, Kopen et al. (1999) demonstrated that MSCs can differentiate into astrocytes after infusion into the central nervous system and it is well known to those skilled in the art that astrocytes secrete factors that support the differentiation and normal function of neurons. Thus, Kopen demonstrates that differentiated MSCs can be used to treat CNS disease especially where astrocytes and their factors provide a therapeutic benefit for treating that disease.

Moreover, Hofstetter et al. (2002, Proc. Natl. Acad. Sci. USA 99:2199-2204), on which Dr. Prockop is co-author, recently demonstrated further post-filing reduction to practice in that MSC treatment improved recovery of animals rendered paraplegic in an art-recognized model of spinal cord injury. Further, MSCs infused into the brain exhibited neuronal morphologies such as rounded cell bodies and distinct processes with growth cone-like terminal expansions. The cells also demonstrated decreased expression of nestin, vimentin and laminin but demonstrated increased expression of NeuN, a neuron-specific marker. Such differentiated cells were termed "neuron-like MSC" and apparently participated in the repair process. These data demonstrate that differentiated MSCs also play a role in providing a therapeutic benefit for treatment of PD, stroke and SCI and further support that claims 16 and 17, indeed, claims 1-3 and 7-18, are enabled in light of the disclosure provided in the specification as filed and in view of the extensive post-filing reduction to practice.

Additionally, Applicants respectfully submit that none of the data in any of the publications cited on any of the animals models clearly establish whether the beneficial effects observed are explained solely by: (i) the MSCs remaining undifferentiated; (ii) the MSCs partially differentiating into cells that have some, but not all, of the phenotypic characteristics of the cells found in the tissue; or (iii) a combination of these events. At this stage, all

interpretations of the data are highly speculative and the data disclosed in these references do not support the Examiner's assertion that claims 16 and 17, reciting using differentiated MSCs, are not enabled by the specification as filed and by post-filing reduction to practice of the invention.

Finally, the Examiner, at page 11 of the Office Action, reiterates that because the physiological art is unpredictable, one cannot assume that results in animal models can be applied in humans. As discussed previously elsewhere herein, art-recognized animal models for parkinsonism, stroke and ischemia, and spinal cord injury have been successfully used to predict the effectiveness of new therapies for human patients with parkinsonism, stroke and ischemia, and spinal cord injury. Applicants respectfully submit that this is all that is required under the patent statute to establish enablement. Otherwise, requiring human clinical data before a new therapy can be patented establishes an unprecedented and almost impossible barrier for developing any new therapies for scores of devastating human diseases.

That is, Applicants respectfully submit that this rejection places an undue burden and will impede progress in the useful arts, rather than promote them as is the directive of the patent statute. Rejection of novel therapies based on the requirement that they be fully tested on humans before they can be patented will impede the development of any new useful therapy. If a new therapy cannot be patented until data from a successful clinical trial are presented, Applicants do not understand how new therapies of any kind, including new drugs, can be developed since, with very few exceptions, safe and carefully planned clinical trials cannot be carried out in most diseases without the investment of large amounts of capital. Few, if any, investors will invest large sums of money if the therapy is not protected by patents.

Thus, by requiring reduction to practice, which is not even required for enablement under Section 112, first paragraph, and further requiring that such reduction to practice be in humans such that clinical data must be obtained before a patent will issue, will effectively prevent development of useful therapies. Investors will not fund the research without a promise of exclusivity in the practice of the therapy so developed. The patent statute was intended to promote such research, not hinder it, and such an interpretation of the enablement requirement is repugnant to the plain meaning of the statute.

For the reasons discussed above, claims 1-3 and 7-18, are amply enabled by the disclosure provided in the specification as filed, as further demonstrated by the extensive post-filing reduction to practice in art-recognized animal models, wherein the models have been

demonstrated to be predictive of successful CNS treatment in humans. Therefore, the rejection of the claims under 35 U.S.C. § 112, first paragraph, for lack of enablement, should be reconsidered and withdrawn.

Summary

Applicants respectfully submit that each rejection of the Examiner to claims 1-3 and 7-18 of the present application has been either overcome or is now inapplicable, and that each of claims 1-3 and 7-20, is in condition for allowance, since claims 19 and 20 have already been deemed to recite allowable subject matter. Reconsideration and allowance of each of claims 1-3 and 7-18 are respectfully requested at the earliest possible date.

Respectfully submitted,

DARWIN J. PROCKOP *ET AL.*

May 28, 2002
(Date)

By: Raquel M Alvarez

RAQUEL M. ALVAREZ, PH.D., J.D.
Registration No. 45,807
MORGAN LEWIS & BOCKIUS, L.L.P.
1701 Market Street
Philadelphia, PA 19103
Telephone No.: 215-963-5000
Direct Telephone: 215-963-5403
Facsimile: 215-963-5299
E-Mail: ralvarez@morganlewis.com

RMA/prw

Enclosures: (Petition for extension of time; supplemental IDS; copy of references listed therein; notice of appeal, and fees associated therewith)